REMARKS

Claims 17, 19, 34, and 51 were previously canceled. Claims 18, 20-33 and 35-50 have been rejoined by the Examiner. Claims 5, 23, and 44 have been amended and Claims 27 and 28 have been canceled. Claims 1-16, 18, 20-26, 29-33, and 35-50 are pending.

Amendments to the Claims

Claims 1, 18, and 36 have been amended to recite specific organic ions. Support for this amendment can be found in Claims 16, 33, and 50, which have been canceled as a result of this amendment to Claims 1, 18, and 36. Claims 1, 18, and 36 have also been amended to recite that the bioactive agent is a "water-soluble bioactive peptide." Support for this amendment can be found in paragraphs 0042 and 0054.

Claims 5, 23, and 40 have been amended to correct a typographical error. Specifically, a comma has been inserted between the words lecithin and vitamin E-TPGS.

Claims 6, 24, and 41 have been amended to clarify that the emulsifying agent is present "in the aqueous phase" at the recited amount. Support for this amendment can be found in the specification at paragraph 0079. Similarly, Claims 8, 26, and 43 have been amended to recite that the concentration of the organic ion refers to the concentration "in the aqueous phase." Support for this amendment can be found in the specification at paragraphs 0059 and 0078.

Claims 13, 31, and 48 have been amended to include various actives from Claims 12, 30, and 37, and to correct their dependency.

Claims 12, 27, 28, 30, 35, and 47 have been canceled.

No new matter has been added by these amendments. Therefore, examination is requested to continue on the claims as amended herewith.

Claim Objections

The Examiner objected to various informalities in the claims. These have been addressed by the amendments presented herewith.

Rejections under 35 U.S.C. § 112

The Examiner rejected Claims 12, 13, 30, 31, 47, and 48 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Specifically, the Examiner contented that the words "synthetic analog" and "synthetic variation" used in these claims does not meet the written description requirement. Claims 12, 30, and 47 have been

canceled, and the objected phrase has been removed from Claims 13, 31, and 48. Thus, withdrawal of this rejection is respectfully requested.

The Examiner Claims 6, 8, 24, 26, 27, 35, 41, and 43 under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subjection matter which Applicant regards as the invention. Specifically, the term "final concentration" in Claims 6, 8, 24, 26, 41, and 43 was alleged to be indefinite because it is not clear which concentration is deemed "final." These claims have been amended to recite that the concentration refers to the concentration in the aqueous phase. This is also how the Examiner interpreted these claims. Withdrawal of this rejection is respectfully requested.

Claims 27 and 35 were also rejected under this section. These rejections are now moot since Claims 27 and 35 have been canceled.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 1, 4, 6-12, and 14-16 under 35 U.S.C. § 102(b) as allegedly being anticipated by Spenlehauer *et al.* (U.S. Patent 6,120,805). Specifically, the Examiner alleged that Spenlehauer teaches the same method recited in the claims. Applicants respectfully traverse this rejection to the extent it relates to the claims as amended herewith.

Spenlehauer teaches a method of preparing microspheres that involves mixing a biodegradeable, biocompatible polymer (*e.g.*, PLGA) with an active in a water immiscible (organic) solvent, then mixing the resulting organic solution in an aqueous solution containing a surfactant (*e.g.*, sodium cholate), and lastly removing the organic solvent to produce the microspheres. (*See* col. 2, ll. 23-30; col. 3, ll. 28-52).

First, Spenlehauer does not disclose a process for preparing microcapsules of water-soluble peptides. The only bioactives listed in Spenlehauer are at column 2, lines 42-49, and water-soluble peptides are not named. In fact, the compound exemplified most in Spenlehauer, *i.e.*, spiramycin, is a non-water soluble macrolide. Thus, because the amended claims recite water-soluble bioactive peptides, they are novel over Spenlehauer.

Second, Spenlehauer does not disclose a process that uses the particular organic ions now recited in the amended claims. The only general description about the contents of the aqueous phase in Spenlehauer is that a surfactant is present (col. 2, l. 63, to col. 3, l. 2). The specific surfactant disclosed and shown in the Examples is cholate, which is not one of the organic ions

recited in amended Claim 1. Thus, because the amended claims recite specific organic ions, the amended claims are novel over Spenlehauer for this additional reason.

Rejections under 35 U.S.C. § 103

The Examiner next rejected claims 2, 3, 5, 18, 20-30, 32, 33, 36-47, 49, and 50 under 35 U.S.C. § 103(a) as allegedly being obvious over Spenlehauer. Specifically, the Examiner contended that the various features recited in these dependant claims, while not expressly disclosed in Spenlehauer, "yield no more than one would expect." Applicants respectfully traverse this rejection to the extent it relates to the amended claims.

The amended claims recite a method for preparing microparticles with a polymer, water-soluble bioactive peptide, and organic ion. None of the bioactives or organic ions recited in the amended claims are disclosed or suggested in Spenlehauer. So even if one were to use the particular arrangement of bioactive, polymer, and organic ion from Spenlehauer, there would be no reason to modify that method by substituting the bioactives and organic ions recited in the amended claims. Further still, even if one were somehow motivated to use the recited bioactives and organic ions in the methods of Spenlehauer, the resulting method does yield more than one would expect.

As detailed in the background of the specification, forming microparticles with water-soluble actives can be problematic, resulting in low loading and efficiency, and high burst. Typical methods to address this problem involved first converting the active into a complex before it is incorporated into the microparticle. The complex does lessen the burst, but requires the extra step of forming the complex. Other methods sought to form an acetate salt of the active, but this resulted in degradation of the active or modification of the polymer. (*See* background of Applicants' specification.) Applicants have addressed the problems in the art by forming certain complexes of water-soluble bioactive peptides *in situ*. That is, the bioactive and polymer are both placed in the organic phase and an organic ion is in the aqueous phase. The two phases are mixed together to form an oil-in-water emulsion. In doing so, the bioactive and organic ion come together and form the complex during microparticle formation. So the claimed method can save the step of having to form a complexes of a water-soluble bioactive peptide beforehand. But there is more than just saving a step.

As noted in the previous Response, the Examiner's attention is drawn to Example 3 of the Applicants' specification where the methods as claimed are exemplified. It was found that the

use of an organic ion in the aqueous phase, and the active and polymer in the organic phase, allowed for greater loading. In Table 6, from the claimed method, the loading was from about 5 to about 17.5%. But in Tables 1-5, from methods where the polymer, active, and ion were all in the organic phase, the maximum loading was 8%, with the averages ranging from 2-6%. *See* also paragraph 0119. Examples 1 and 2 also detail certain experiments where the organic ion is not one of those recited in the present claims. Thus, the comparison in Table 6 to Tables 1 and 3 is also relevant in this regard.

Still further, the amount of active release is lower when one uses a method where the active, ion, and polymer are all in the organic phase, as compared to the claimed method where the ion is in the aqueous phase (compare Table 2 with Table 6). Accordingly, the claimed methods result in compositions with more desirable properties (*e.g.*, loading and amount released) that other methods. As such having the organic ion in the aqueous phase and the active and polymer in the organic phase is not merely a routine optimization. The advantages of the claimed method are real, have been demonstrated and described in the application, and were certainly not taught or suggested by Spenlehauer. In light of the above, withdrawal of the rejection under 35 U.S.C. 103 is respectfully requested.

The Examiner next rejected claims 13, 31, and 48 under 35 U.S.C. § 103(a) as allegedly being obvious over Spenlehauer in view of Alfven (WO98/43660). Specifically, the Examiner notes that Spenlehauer discloses a method of making a microparticle where the polymer and active are in the organic phase, and an organic ion (e.g., cholate) is in the aqueous phase. The Examiner notes, however, that Spenlehauer does not disclose the active oxytocin. For this feature the Examiner cites Alfven, which disclose the use of oxytocin. Applicants respectfully traverse this rejection.

The Examiner wrongly asserts that it would have been obvious to use the method of Spenlehauer to make microparticles of Alfven's oxytocin. Simply using Splenhauer's method with oxytocin would still not result in the claimed method. The method would have to be modified by using the certain organic ions recited in the amended claims. Neither Spenlehauer nor Alfven give any reason to make such a modification. One would have to have chosen the particular arrangement of components used in Spenlehauer, decided to try that method with water-soluble peptides (like the oxytocin of Alfven or others), and use the certain ions recited in

the claims. This requires too much picking and choosing and evidences the non-obviousness of the claimed methods.

Enclosed herewith is payment in the amount of $1,30.00, which includes the $130.00 fee under 37.C.F.R. §1.17(a)(1) for the One-Month Extension of Time and the $180.00 fee under 37.C.F.R. §1.17(p) for the Supplemental Information Disclosure Statement. No additional fees are believed due; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

BALLARD SPAHR LLP

/Christopher L. Curfman/

Christopher L. Curfman
Registration No. 52,787

BALLARD SPAHR LLP
Customer Number 23859
(678) 420-9300 (Phone)
(678) 420-9301 (Facsimile)

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I hereby certify that this correspondence, including any items indicated as attached or included is being submitted electronically via EFS-WEB submission, on the date indicated below.

/Christopher L. Curfman/	March 17, 2010
Christopher L. Curfman	Date